U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Alessandra Rinaldi
BioActor B.V./Solabia Nutrition
Gaetano Martinolaan 50
Maastricht, Limburg, Netherlands 6229 GS

Re: GRAS Notice No. GRN 001226

Dear Ms. Rinaldi:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001226. We received BioActor B.V./Solabia Nutrition (BioActor)'s notice on August 15, 2024, and filed it on February 5, 2025. BioActor submitted an amendment to the notice on April 11, 2025, clarifying the specifications, analytical methodology, dietary exposure, and technical effect, and providing an updated literature review.

The subject of the notice is sweet orange (*Citrus sinensis* L. Osbeck) fruit extract (sweet orange extract) for use as an ingredient in flavored milk and imitation milk drinks; dry powdered milk mixtures; yogurts; coconut beverages; cookies; cereals; cereal, granola, and nutrition bars; fruit, fruit-flavored, and vegetable juices and drinks; table fats and vegetable oils; chocolate and dietetic candies; teas; carbonated soft drinks; “fortified” waters; nutrition drinks; nutrition powders; “energy” drinks; and “sport” drinks at a level of 500 mg per serving.[1]

Our use of the term, “sweet orange extract,” in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA’s labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for non-standardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Nutrition Center of Excellence (NCE). The Office of Pre-Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for “sweet orange extract.”

BioActor describes sweet orange extract as a light brown to yellow powder, prepared from the immature, dried fruits of sweet oranges (*C. sinensis* L. Osbeck), containing ≥90% hesperidin (CAS Registry Number 520-26-3, $C_{28}H_{34}O_{15}$) and small amounts of isonaringin, neoponcirin, and hesperetin.

BioActor describes the method of manufacture of sweet orange extract. Immature whole orange fruits are dried, ground, and extracted with alkaline

water containing calcium chloride and calcium hydroxide. The resulting aqueous extract is filtered, and the filtrate is treated with sulfuric acid to precipitate hesperidin. This precipitate is then washed, filtered, dried, micronized, and heated to produce the final sweet orange extract. BioActor states that sweet orange extract is manufactured according to current good manufacturing practices and that all raw materials and processing aids are food grade and are used in accordance with applicable U.S. regulations and are GRAS for their intended uses.

BioActor provides specifications for sweet orange extract that include total bioflavonoids (93%), hesperidin (≥90% on dry weight (DW) basis), (2S)-hesperidin (≥70% on DW basis), sulphated ash (≤0.5%), loss on drying (≤5%), lead (≤0.1 mg/kg), arsenic (≤0.05 mg/kg), cadmium (≤0.05 mg/kg), mercury (<0.1 mg/kg), benzo(a)pyrene (<0.01 mg/kg), sum of benzo(a)pyrene, benzo(a)anthracene, benzo(b)fluoranthene and chrysene (<0.05 mg/kg), and limits for microorganisms. BioActor provides the results from the analyses of five non-consecutive batches to demonstrate that sweet orange extract can be manufactured to meet these specifications. Based on the stability testing results, BioActor concludes that sweet orange extract is stable for 36 months when stored at 25 °C and 60% relative humidity in a dark, sealed container.

BioActor discusses the eaters-only cumulative dietary exposure to hesperidin reported in GRN 000796[2] that included both background diet and intended uses and was based on food consumption data from the 2013-2014 National Health and Nutrition Examination Survey (NHANES). BioActor states that the eaters-only cumulative dietary exposure to hesperidin for the U.S. population aged 2 years and older is estimated to be 1,5 mg/person (p)/d (22.3 mg/kg body weight (bw)/d) at the mean and 3,1 mg/p/d (44.3 mg/kg bw/d) at the 90th percentile. BioActor notes that the intended uses of sweet orange extract are substitutional, on a hesperidin basis, for the uses of orange extract described in GRN 000796 and therefore, the cumulative dietary exposure to hesperidin is not expected to increase.

BioActor discusses data and information relevant to the safety of hesperidin, the major constituent in sweet orange extract. BioActor notes that *C. sinensis* L. Osbeck is the most common and important species among citrus fruits. BioActor compares the hesperidin content of sweet orange extract to that of orange extract, noting that sweet orange extract contains comparable levels to orange extract (sweet orange extract >90% vs. ≥85% for orange extract). To support the safety of hesperidin, BioActor cites the conclusion of the 1982 Select Committee on GRAS Substances that there is no published safety information that would indicate that a safety hazard exists when hesperidin is used at the exposure levels estimated at that time. BioActor also notes that a subchronic study using methyl hesperidin, a compound structurally similar to hesperidin, was conducted in B6C3F1 mice at doses of 0%, 0.3%, 0.6%, 1.25%, 2.5%, and 5.0% of the diet (Kurata Y et al, 1990). Based on the study findings, the no observed adverse effect level was determined to be 5.0%, the highest dose tested. As additional evidence of safety, BioActor discusses a 13-week toxicity study in Sprague Dawley rats following the Organisation for Economic Co-operation and Development

(OECD) guidelines (Li Y, et al., 2019) on hesperidin isolated from orange peel that showed that hesperidin at doses of 250 and 500 mg/kg did not induce any abnormalities in body weight, food consumption, clinical signs, ophthalmological and neurological observations, urine analysis, hematology, clinical chemistry, organ weights, and gross pathology. BioActor also states that numerous *in vitro* studies have been conducted that show that hesperidin is non-mutagenic and not genotoxic. As corroborative support for safety, BioActor cites human studies on hesperidin that did not show any adverse effects.

Based on the totality of the data and information, BioActor concludes that sweet orange extract is GRAS through scientific procedures under the conditions of its intended use.

Standards of Identity

In the notice, BioActor states its intention to use sweet orange extract in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing sweet orange extract bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of ONFL in NCE. OPMAS did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, BioActor describes sweet orange extract as a light brown to yellow powder. As such, the use of sweet orange extract in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the

definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 001226 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OPMAS.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of BioActor's notice concluding that orange extract is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing orange extract. Accordingly, our response should not be construed to be a statement that foods containing orange extract, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that BioActor provided, as well as other information available to FDA, we have no questions at this time regarding BioActor's conclusion that sweet orange extract is GRAS under its intended conditions of use. This letter is not an affirmation that sweet orange extract is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001226 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2025.06.09 12:02:30 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety

Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program

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1. ^ BioActor states that sweet orange extract is not intended for use in infant formula, in products under the jurisdiction of the United States Department of Agriculture, or in food where the standards of identity would preclude its use.
2. ^ The subject of GRN 000796 is orange extract containing ≥85% hesperidin. We evaluated GRN 000796 and responded in a letter dated February 20, 2019, stating that we had no questions at that time regarding the notifier's GRAS conclusion.